Termination of Reentrant Propagation by a Single Extracellular Stimulus in an Atrial Ring Model

C.R. Johnson, R.C. Barr
Department of Biomedical Engineering, Duke University, NC, USA

Abstract-Cardiac reentry, the underlying mechanism of both tachycardia and fibrillation, is often terminated clinically with extracellular stimuli. We developed a one-dimensional mathematical model to find the probability that a short, randomly-timed extracellular stimulus would terminate reentry and to study the mechanisms responsible for termination. Our ring model consisted of 100 atrial cells, with the cell membrane represented mathematically by a model developed by Nygren *et al.* Stable reentry was established, and then a single extracellular stimulus with a pulsewidth of either 2.5 msec or 5.0 msec was applied through a cathode positioned over cell 25 and an anode over cell 50. Total delivered charge was kept constant. The timing of the stimulus was varied in 1.0 msec steps so as to sample one complete revolution of the reentering wavefront. The probability that the 2.5 mec stimulus would terminate reentry was 2.8%, 0.2% at the cathode and 2.6% at the anode. The probability of termination increased to 4.2% with the 5.0 msec stimulus (1.5% at the cathode and 2.7% at the anode). The anode was more significant than the cathode in terminating reentry, and the anodal mechanism was less sensitive to the stimulus pulsewidth.
Keywords - Electrophysiology, Reentry, Electrical Stimulation

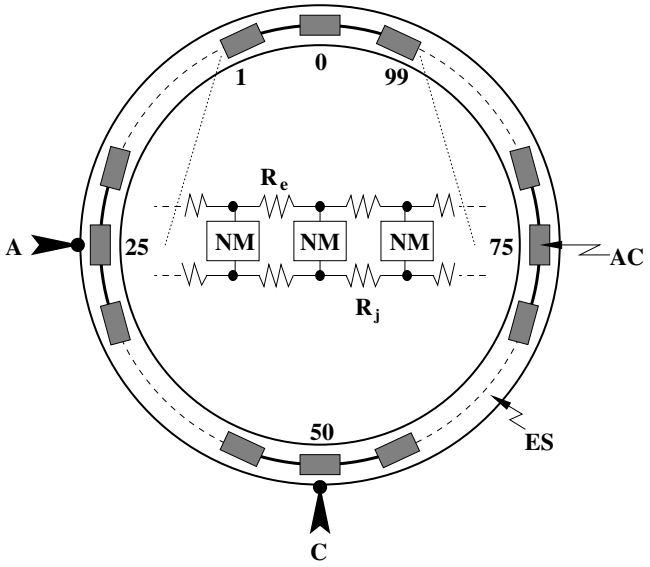

Fig. 1. Ring model consisting of 100 atrial cells. The diagram in the center of the ring shows the equivalent electrical circuit for cell 0 and its two neighboring cells (AC, atrial cell; ES, extracellular space; R_e, extracellular resistance; R_j, junctional resistance; NM, Nygren membrane). Extracellular electrodes are positioned at cell 25 and cell 50 (C, cathode; A, anode).

I. Introduction

Cardiac reentry is believed to be the primary mechanism underlying the maintenance of tachycardia and fibrillation in the heart, both in the ventricle and the atria. In an attempt to terminate or modify reentrant excitation, extracellular stimuli are often used; these interventions may or may not work, for reasons that are often unclear. One difficulty is that a number of seemingly straightforward questions about the interaction of the fields produced by the stimuli with the propagating wavefronts are unanswered in the literature. For example, what is the probability that a short, randomly-timed stimulus will terminate excitation in a reentrant loop? By what mechanisms is termination possible?

While reentry in the whole heart is most likely a three-dimensional phenomenon, the simplest manifestation is continuous excitation around a thin ring of tissue (approximately one-dimensional). Many investigators have explored this type of reentry in a wide range of experimental preparations [1–5]. These preparations can also be modeled mathematically, and, with the aid of computers, the dynamics of a reentrant loop can be observed in detail. Despite the advantage of providing for a more thorough analysis, much of the past theoretical work has used simplified models of the membrane ionic currents (*i.e.* Fitzhugh-Nagumo) [6–8], ignored the importance of intercellular coupling (gap junctions) [9,10], or relied upon unrealistic methods for stimulation (*i.e.* injecting current intracellularly as opposed to having electrodes positioned in a restricted extracellular space) [9–13]. While much has been learned about reentry and its termination from such models, it is useful to compare those findings to results from more physiologically accurate membrane models, within a more realistic structure, and under more clinically relevant stimulation protocols.

II. Methods

A. Atrial Ring Model

We developed a one-dimensional ring model consisting

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Table I

Termination of reentry by an extracellular stimulus for two pulsewidths. The ranges of stimulus times that terminated reentry and the width of the resulting termination windows are shown for both cathodal (τ_c) and anodal (τ_{a1},τ_{a2},τ_{a3}) stimulation. $\mathcal{P}_c$ and $\mathcal{P}_a$ are the resulting probabilities that a randomly-timed stimulus will terminate reentry at the cathode and anode, respectively. $\mathcal{P}_T = \mathcal{P}_c + \mathcal{P}_a$.

δ_{stim} (msec)	τ_c (msec)	$\mathcal{P}_c$	τ_{a1} (msec)	τ_{a2} (msec)	τ_{a3} (msec)	$\sum_{i=1}^{3} \tau_{ai}$ (msec)	$\mathcal{P}_a$	$\mathcal{P}_T$
2.5	216.8 − 218.4 (1.6)	0.2%	105.2 − 112.6 (7.4)	113.0 − 121.4 (8.4)	124.0 − 126.0 (2.0)	17.8	2.6%	2.8%
5.0	201.1 − 211.4 (10.3)	1.5%	103.8 − 111.7 (7.9)	112.1 − 121.2 (9.1)	123.3 − 125.1 (1.8)	18.8	2.7%	4.2%

of 100 atrial cells to study the likelihood that a short extracellular stimulus would terminate reentrant propagation (Fig. 1). The cell membrane was represented mathematically by a model developed by Nygren *et al* [14]. Each cell, 130 μm long and 11 μm in diameter, was assumed to be isopotential [15,16]. The gap junctions connecting the intracellular space of neighboring cells were represented by one hundred 50 ρS connexons in parallel; this resulted in a total junctional resistance R_j of 200 $M\Omega$. The total extracellular resistance R_e between cells was 21.1 $M\Omega$, based on an interstitial volume of 0.8 ρL and an extracellular resistivity of 100 $\Omega \cdot cm$. The resulting mathematical equations were solved using an explicit method (Forward Euler) with a temporal discretization Δt_s of 25 μsec (t_s, simulation time).

B. Initiating Reentry

Reentry was initiated by stimulating one end (cell 0) of an 100 cell *fiber*; as the resulting wavefront propagated down the fiber, the two ends were mathematically connected to form a ring. The wavefront returned to cell 0, which had recovered from its initial excitation, and continued uninterrupted around the ring. We allowed reentry to continue for 10 seconds so that the underlying dynamics could reach a steady-state. In this time, the wavefront, propagating at 1.88 cm/sec, made approximately 14.5 revolutions. The final model state variables (at $t_s = 10.0$ sec) were recorded to use as the initial conditions for subsequent simulations.

C. Stimulation Protocol

Simulations, 2.5 $msec$ in duration, were performed to measure the probability that a single extracellular stimulus would terminate the reentrant wavefront. The stimulus was applied through a cathode positioned over cell 25 and an anode positioned over cell 50 (Fig. 1). We tested pulsewidths δ_{stim} of 2.5 $msec$ and 5.0 $msec$. The stimulus current I_{stim} was set to 15400 ρA and 7700 ρA respectively to maintain a constant total delivered charge Q_{stim} of 38.5 ρC ($Q_{stim} = \delta_{stim} \cdot I_{stim}$). The timing of the stimulus was incremented by 0.1 $msec$ between simulations until one complete revolution of the reentering wavefront was sampled. The transmembrane potentials from each cell were recorded to determine whether the stimulus did or did not terminate reentry, and at which electrode.

III. Results

Table I summarizes the results of our simulations. Both cathodal and anodal stimulation terminated reentry for each pulsewidth. For a δ_{stim} of 2.5 $msec$, the probability that a randomly-timed stimulus would terminate reentry was 2.8%; for a δ_{stim} of 5.0 $msec$, the probability increased to 4.2%. The greater likelihood that the 5.0 $msec$ stimulus would terminate reentry was mainly due to differences at the cathode. However, for each pulsewidth, the probability of terminating reentry at the anode was greater than the probability of terminating reentry at the cathode.

A. Termination at the Cathode

Fig. 2A shows the timing of the stimulus relative to the waveform at cell 25 (the position of the cathode) that resulted in termination of reentry. If the cathodal stimulus was timed such that the membrane in the *antegrade* (counterclockwise) direction was refractory but the membrane in the *retrograde* direction was sufficiently recovered, the result was a single propagated secondary wavefront in the retrograde direction (unidirectional block); and when this secondary wavefront collided with and annihilated the primary reentering wavefront, reentry was terminated and the entire ring returned to a resting state. Bidirectional propagation occurred if the cathodal stimulus interacted with recovered, excitable membrane in both the antegrade and retrograde directions; the resulting secondary retrograde wavefront annihilated the primary wavefront as above, but the secondary antegrade wavefront continued unimpeded around the ring, essentially advancing the reentry. If the cathodal stimulus was delivered over more refractory membrane, block occurred in both directions, and the stimulus had no visible effect on the reentering wavefront.

The separate termination windows (τ_c) for each

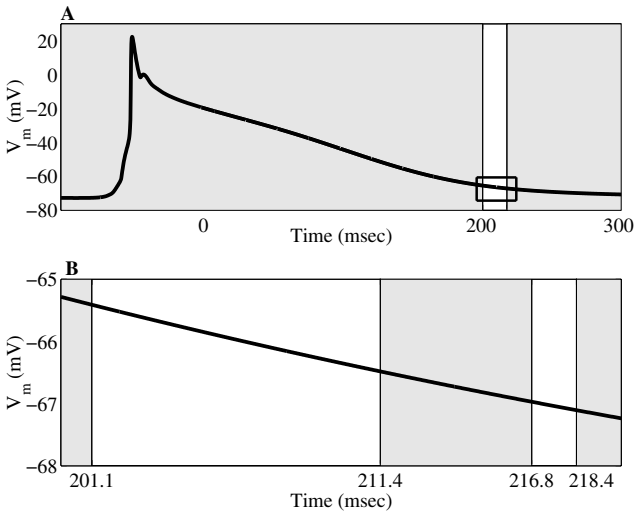

Fig. 2. (A) Transmembrane potential at cell 25, the location of the cathode. The white band extends to the outer boundaries of the cathodal termination windows (τ_c) for the two stimulus pulsewidths, showing the timing of the stimulus relative to the propagating wavefront necessary to terminate reentry at the cathode via unidirectional block. (B) The area in (A) outlined by the small rectangle, detailing the separate termination windows for the 2.5 *msec* stimulus (216.8−218.4 *msec*) and the 5.0 *msec* stimulus (201.1−211.4 *msec*).

pulsewidth are shown more clearly in Fig. 2B, providing a graphical representation of the data summarized in Table I. The probability of termination at the cathode with a 2.5 *msec* stimulus was significantly less than the probability of termination with a 5.0 *msec* stimulus (0.2% versus 1.5%).

B. Termination at the Anode

Fig 3. shows the timing of the stimulus relative to the waveform at cell 50 (and the two neighboring cells) that terminated reentry at the anode, which was positioned over cell 50. The highlighted band in Fig. 3 extends from the beginning of the first termination window (τ_{a1}) for the 5.0 *msec* stimulus to the end of the last termination window (τ_{a3}) for the 2.5 *msec* stimulus (see Table I). If the leading edge of the wavefront was propagating into cell 49, 50, or 51 at the time the stimulus was delivered, the primary wavefront was blocked and reentry was terminated; otherwise, the anodal stimulus had little or no effect on reentrant propagation.

Unlike at the cathode, the probability of terminating reentry at the anode was similar for both pulsewidths (2.6% for the 2.5 *msec* stimulus; 2.7% for the 5.0 *msec* stimulus). The locations of the three termination windows (τ_{a1}, τ_{a2}, τ_{a3}) in time for each pulsewidth were also very similar (Table I). We investigated the potential waveforms around the anode at the time of the stimulus in more detail and found that stimuli delivered during τ_{a1} prevented the excitation of cell 49, stimuli delivered during τ_{a2} prevented the excitation of cell 50, and stimuli delivered during τ_{a3} prevented the excitation of cell 51.

IV. Discussion and Conclusion

The mechanism by which a properly timed depolarizing (cathodal) stimulus can result in the unidirectional block of the elicited wavefront, and the importance of this mechanism in both the *initiation* and termination of reentry, is well represented in the literature [2,7,8,12, 13,17–22]. However, what is less well understood is the ability of an anodal stimulus to terminate reentrant propagation. We found the anodal mechanism to be more significant than the cathodal mechanism, as well as less sensitive to the pulsewidth of the delivered stimulus.

These results need to be extended to include additional stimulus waveforms. But it is clear from these limited cases that developing protocols to more effectively terminate reentrant propagation in the heart will require a more complete understanding of how anodal stimuli interact with the surrounding tissue.

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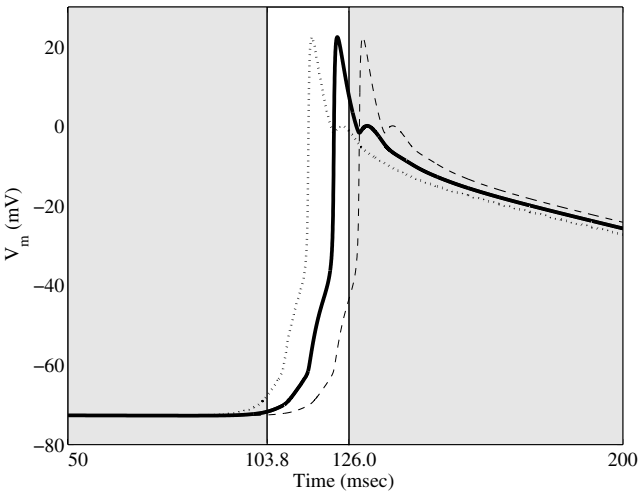

Fig. 3. Transmembrane potential at cell 49 (dotted line), cell 50 (solid line), and cell 51 (dashed line). The anode is positioned over cell 50. The white band extends to the outer boundaries of the anodal termination windows (τ_{a1} through τ_{a3}), roughly illustrating the timing of the stimulus relative to the propagating wavefront required to terminate reentry at the anode.

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